Women with a positive HPV test can safely have yearly surveillance rather than immediate colposcopy

Cuzick J, Szarewski A, Cubie H, et al. Management of women who test positive for high-risk types of human papillomavirus: the HART study. Lancet 2003; 362: 1871–1876.

OBJECTIVE To compare the test characteristics of human papillomavirus (HPV) testing and cytological screening for the detection of high-grade cervical intraepithelial neoplasia (CIN) and to determine if surveillance at 12 months is as effective as immediate colposcopy for women with positive HPV results and/or borderline cytology results.

DESIGN Cross-sectional study with randomized controlled trial within a subgroup. Allocation was done centrally and was blocked.

SETTING A total of 161 family practices and five referral centres in the UK.

SUBJECTS A total of 10,358 women, aged 30–60 (mean 42) years, who had not had an abnormal cytology result in the previous 3 years and had never been treated for CIN, were screened by cytology and HPV testing for high risk types. Women with mild dyskaryosis or worse (n=213, 2%) were referred for immediate colposcopy. Women with minimal abnormality (borderline cytology results and/or positive HPV results, n=825, 8%) were included in the randomized trial.

INTERVENTION Randomization allocated 411 women to the surveillance group (cytological and HPV testing at 6 and 12 mos, with colposcopy at 12 mos for all women) and 414 women to the immediate colposcopy group.

MAIN OUTCOME MEASURES Diagnostic test properties, incidence of CIN2 or worse, colposcopy rate.

MAIN RESULTS There were 90 cases of CIN2+ detected overall. The diagnostic test properties are shown in Table 1. In the randomized trial, 29% of women, a similar proportion in each group, did not attend for further testing. The proportions of women with CIN2+ detected were similar in the surveillance and immediate colposcopy groups (2.2% and 2.7%, respectively, p=0.66*), but fewer cases of CIN1 were detected in the surveillance group (3.9 vs 7.5%, p=0.04). No case of invasive cervical cancer was identified. All cases of CIN2+ in both groups were HPV positive at enrolment and all cases in the surveillance group continued to be HPV positive at 6–12 months. Regression of HPV occurred in 42% of HPV positive women in the surveillance group. Compared with immediate referral, surveillance for 1 year, with colposcopic referral restricted to women with persistent HPV positivity or cytological abnormalities, would more than halve the rate of colposcopy.

CONCLUSION Initial testing for high risk HPV types was more sensitive, but less specific, than cervical cytology for detection of high-grade cervical lesions. For women with borderline cytology and/or positive HPV results, a policy of yearly surveillance resulted in a lower colposcopy rate than a policy of immediate colposcopy, with no increased risk of high-grade cervical lesions or cancer.

* Calculated from data in article.

Table 1
Diagnostic test properties for detecting CIN2 or worse

Test	Sensitivity	Specificity	Positive predictive value
Cytology ⩾borderline	77	96	16
Cytology ⩾mild dyskaryosis	70	99	34
HPV ⩾1 pg/mL	97	93	13
HPV ⩾2 pg/mL	96	94	15
Cytology ⩾mild or HPV ⩾2 pg/mL	100	94	14

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Commentary

Cervical infections by approximately 15 cancer-associated (oncogenic) human papillomavirus (HPV) types cause virtually all cervical cancer worldwide. However, HPV infections are quite common, with most women being exposed during their lifetime. HPV infections, even by oncogenic types, are typically transient and often cause no detectable, or only mild, cervical abnormalities. In some women, infections persist and these women are at the greatest risk of cervical cancer and its immediate precursor, cervical intraepithelial neoplasia grade 3 (CIN3).

Based on knowledge of the central role for persistent, oncogenic HPV in cervical carcinogenesis, one test for HPV DNA has already been developed (Hybrid Capture 2 [HC2]) and others will soon be widely available. HPV negativity suggests a very low risk of prevalent or incipient cancer/CIN3, but single-time HPV positivity does not necessarily imply persistence leading to a high risk of neoplastic progression. As a result, the optimal use of HPV tests, either in conjunction with or instead of cytological (Pap smear) screening, has not been fully evaluated. There are ample prospective data to suggest that a single baseline HPV DNA test is more sensitive than a single conventional Pap smear for the detection of CIN3 or cancer (CIN3+) over 5–10 years.[1,2] Also, one randomized trial demonstrated that HPV DNA testing is a useful triage of equivocal/borderline/atypical squamous cells of unknown significance cytology.[3] Accordingly, HPV testing has now been approved, in the United States, as an adjunct to cytology for triage and for general screening in women $\geqslant$ 30 years old. However, formal evaluations are lacking regarding the optimal management of the many millions of women that will soon be found to be HPV positive but cytologically normal.

The HART (HPV in Addition to Routine Testing) study was a multicentre, randomized trial to evaluate HPV DNA testing using HC2 in conjunction with conventional Pap smears for general cervical cancer screening. The study targeted 11,085 women aged 30–60 years old in recognition that the median age of CIN3 is the late 20's to early 30's and that cervical cancer is slow to develop from the precancerous stage. Women who were HPV positive and/or had borderline cytology were randomized to either immediate colposcopy or surveillance with repeat testing at 6–12 months and exit colposcopy at 12 months. The design appropriately included colposcopy of a sample of women negative by HC2 and Pap smears to assess false negative test results.

The authors of the present study reported that a single HC2 test, positive at the 1.0 pg/mL cutpoint recommended by the US Food and Drug Administration, was significantly more sensitive and less specific than a Pap smear at the cutpoint of either borderline abnormality or mild abnormality. Weighing sensitivity and specificity equally, HC2 was more accurate than the Pap smear. HC2 had greater negative predictive value (women who were test negative were more likely to be without CIN2+) and less positive predictive value (women who were test positive were less likely to have CIN2+) than the Pap smear. Using a 2.0 pg/mL cutpoint for HC2, there was the expected tradeoff in reduced sensitivity and increased specificity[4], with concomitant increase in positive predictive value. Combinations of tests for HC2 (2.0 pg/mL cutpoint) and cytology (mild abnormality cutpoint) could achieve a 100% sensitive screen with similar specificity as HC2 at the 2.0 pg/mL cutpoint.

More importantly, this study demonstrated that a follow-up interval of 6–12 months with retesting of women with positive HC2 results or borderline abnormal cytology could reduce colposcopic referral by allowing about 40% of transient infections to regress (HC2 negative). Although HC2 does not discriminate the types that are infecting, the majority of double positive HC2 over a 1-year time period represent type-specific persistent HPV infection (Castle, unpublished results), an important discriminator of risk among HPV exposed women.[5] However, this gain in screening specificity must be weighed against a $\sim$25% loss to follow-up during that interval.

We note that 80 of 90 (88.9%) CIN2+ cases identified in the study had HC2 signals $\geqslant$ 10 pg/mL. Although using a $\geqslant$ 10 pg/mL cutpoint results in an improved clinical specificity, the losses in sensitivity are likely to be unacceptable. However, in the context of repeat HC2 testing, it might be used to discriminate risk, especially in the absence of co-testing by cytology. For example, those women who have HC2 signals $\geqslant$ 10 pg/mL could be referred for immediate colposcopy, whereas those women who have 1–9.99 pg/mL signals could be recommended for a 6 to 12-month follow-up with retesting. These lower HC2 signal strengths are common in women with negative cytology[4] who were included in the follow-up study arm in this study. It will be an important ancillary analysis to examine what the signal strengths were at the time of repeat testing.

Although the authors pointed out that a more sensitive test may permit longer intervals of screening, the dropout of participants observed in this study between screening and colposcopic referral or a follow-up visit raises a cautionary flag as to the consequences of multi-stage screening. Identification of new biomarkers of risk of HPV persistence and neoplastic progression, leading to a second paradigm shift from HPV detection to cervical cancer risk identification, could circumvent many of these concerns.

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